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RESEARCH**

APPLICATION NUMBER:
sBLA 125057/110

CROSS DISCIPLINE TEAM LEADER REVIEW

HUMIRA BLA 125057
Cross-Discipline Team Leader Review

Date	December 20, 2007, Last Revised: January 15, 2008
From	Markham C. Luke, M.D., Ph.D., Lead Medical Officer, Dermatology <i>M. Luke 1/15/07</i>
NDA/BLA #	BLA 125057
Supplement#	Supplement 110
Applicant	Abbott Laboratories
Date of Submission	March 23, 2007
PDUFA Goal Date	January 21, 2008
Proprietary Name / Established (USAN) names	Humira (Adalimumab)
Dosage forms / Strength	Pre-filled syringe 40 mg Self-injecting pen 40 mg
Proposed Indication(s)	Efficacy Supplement for additional indication: Treatment of adult patients with moderate to severe chronic plaque-type psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
Recommended:	Approval

1. Introduction

Humira (adalimumab) is currently approved for other indications, i.e. rheumatoid arthritis (initially approved in 2002), psoriatic arthritis, ankylosing spondylitis, and most recently Crohn's disease. Humira is a member of the class of antibody drug products known as TNF-alpha inhibitors.

Two other TNF-alpha inhibitors are currently approved for treating chronic plaque psoriasis, Enbrel (etanercept) and Remicade (infliximab). Enbrel was approved for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy in 2004.

Remicade was approved for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate in 2006. When Remicade was approved for the plaque psoriasis indication, a Medication Guide was implemented as a Risk Management Tool due to concern regarding increased potential for serious and opportunistic infections in patients treated with Remicade.

2. Background and Comments on Plaque Psoriasis

Plaque psoriasis is a dermatologic disease that is not generally considered to be serious or life-threatening. Unlike its rheumatologic counterpart, psoriatic arthritis, plaque psoriasis does not leave permanent local sequelae from the disease itself. Healed skin lesions may have some pigmentation changes, but those too resolve over time. On the other hand, plaque psoriasis does impart to patients with the disease, social stigmata that affect their day-to-day functioning, especially when the disease is sufficiently severe.

Systemic therapy for psoriasis, in general, is reserved for those patients in whom disease is more widespread and less amenable to local application of topical therapies. Systemic therapies for plaque psoriasis include methotrexate, acetretin, PUVA therapy, cyclosporine, alefacept, efaluzimab, and the TNF inhibitors: etanercept and infliximab. Adalimumab would be yet another TNF-inhibitor. Each of the TNF inhibitors have a slightly different safety profile, but in general, each inhibits the immune system resulting in some effect on plaque psoriasis.

3. CMC/Device

No CMC concerns are raised by this Efficacy supplement as the currently approved drug product is being used without modification for the psoriasis indication.

No device concerns were raised by the Product reviewer, Dr. Gupreet Gill-Sangha. In the psoriasis trials, subjects were treated using pre-filled syringes, but the applicant seeks approval and labeling for the psoriasis indication with both the pre-filled syringe and an autoinjector Pen. The autoinjector unit is a disposable drug product in which the functional packaging (syringe) is integrated into an autoinjector Pen. Thus, no concerns were raised with regard to any change in product quality by the ONDQA reviewer.

Of note Humira Pen was noted to be more acceptable than the pre-filled syringe alone to subjects in a use study conducted in rheumatoid arthritis patients. Whether this results in any safety or efficacy differences when used in place of the pre-filled syringe was not studied. However, from a regulatory perspective, we are informed that no use studies were required for the Crohn's indication per the GI Team Leader, Dr. John Hyde, and it was the understanding of the rheumatology Team Leader, Dr. Jeffrey Siegel, that the use studies for the Pen in RA patients were reviewed in the context that they would be applicable to any other indication, such as the new psoriasis indication.

As indicated in the Product review, "CDRH provided a consult for 125057- and found the pen in compliance with current standards." b(4)

4. Nonclinical Pharmacology/Toxicology

Review by the Pharmacology/Toxicology reviewer, Dr. Carmen Booker reveals "No safety pharmacology concerns" and no nonclinical safety issues relevant to the clinical use of adalimumab. No information from Dr. Booker's review contradict the Pregnancy Category B that is currently in place for Humira.

Of interest, Dr. Booker points out that several cross-reactivity studies revealed that adalimumab binds to the vascular and intrinsic muscle of multiple tissues. The clinical significance of this finding is not known.

Humira has a pregnancy registry in place with a current pregnancy category of B.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewer, Dr. Tien-Mien Chen, reviewed the pharmacokinetic profile of adalimumab and Anti-adalimumab antibody formation. Dr. Chen performed a question based review of the submission and made the following determinations:

- 1) Adalimumab mean steady-state serum trough levels were in the range of those observed in studies for other indications.
- 2) The rate of anti-adalimumab antibody (AAA) formation in patients with psoriasis was 8.4% and is in the range of that observed for other indications. Of note, this study was conducted in a study with at least one blood sample taken after the first adalimumab dose. It is not clear if this rate is higher with repeated dosing of adalimumab from Dr. Chen's review.
- 3) Patients with AAA formation had lower response rate, i.e. had less success with adalimumab treatment. For example, the PASI 75 response rate in AAA+ patients was only 11 %, where as it was close to 76% in AAA- patients.
- 4) AAA+ did not have any apparent impact on the safety of adalimumab.
- 5) The long term effects of AAA+ was not evaluated.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Humira was found to be effective for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.

The Clinical and Biostatistics Reviews by Dr. Denise Cook and Dr. Clara Kim both agree on this point. The results from the clinical trials demonstrated statistical and clinical significance of response to treatment with Humira in those patients with moderate to severe chronic plaque psoriasis.

Of note, patients who had mild disease at baseline were inadvertently entered into the study. Those patients were excluded from the trial results by the Agency reviewers with the modified numbers reflected in the labeling. Further, efficacy of Humira when compared to placebo was demonstrated in both short term (16 week) and longer term (1 year) evaluations.

Subgroup evaluations for severity maintained the conclusion that Humira was efficacious for both moderate and severe chronic plaque psoriasis.

The key concerns and focus for efficacy discussion for this application revolved around study design issues and interpretation of the results of a study that was not originally reviewed by DDDP and with minimal input by DDDP into original study design.

PASI vs. PGA

In evaluating efficacy of psoriasis, two main scoring systems have been used: Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA). While PASI tries to assess global severity it is limited by the following:

- 1) It is non-intuitive and does not correlate with clinical understanding of the disease. The scale is almost never used in clinical practice. No dermatologist or general practitioner records PASI score with each visit.
- 2) The endpoint assessment is dynamic rather than static as it relies on a comparison to baseline with a percentage improvement. The percentage improvement is problematic due to a skin assessment bias of a clinician bias towards non-linear correlation between lesions and severity.
- 3) The PASI scale goes from 0 to 96. However, moderate to severe psoriasis is defined in many studies for inclusion as PASI >12. This suggests a very non-linear assessment of psoriasis severity which adds to the relative non-intuitiveness of this assessment. The upper end of this scale is hardly ever used.

PGA scales are currently recommended by DDDP for use as the primary endpoint or as a co-primary endpoint with PASI. The PGA scale used by Abbott for these studies was less than perfect as the Clear assessment was not entirely "clear". Of note both Clear and Almost Clear allowed for moderate erythema. This is not allowed in other PGA scales for psoriasis. We will \checkmark for Humira and will not allow future use of scales with such magnanimous interpretation of Clear. The PGA scale used for Humira was not originally reviewed by the current review team or the current review Division.

Regardless, the PGA scale was considered as a co-primary endpoint in evaluating Humira for efficacy. This is the first biologic drug product that allowed for such an evaluation due to the presence of the PGA, which was recommended by the Agency in meetings with the applicant. This Division and this reviewer did provide input into the use of PGA to the then reviewing Division, which was acted upon.

An EMEA guideline on psoriasis studies recommends that PASI not be used as the sole primary endpoint for evaluation of plaque psoriasis. The FDA, while not having published any such guidance has received advice to this regard from a 1997 Advisory Committee on psoriasis endpoints. Currently, DDDP recommends to applicants that PASI not be used as the sole primary endpoint and instead that a qualified and agreed upon PGA be used.

Long-term Evaluation

The trial design for the efficacy studies included a longer-term evaluation of efficacy. One of the trials was divided into three periods: A, B, and C. Period A evaluated efficacy at 16 weeks by randomized assignment to adalimumab or placebo. Period B included those patients who attained a 75% response in PASI or better (PASI 75) and those patients received 40 mg every other week of adalimumab up to week 33. Period C is a double-blind placebo-controlled treatment period up to 52 weeks in which subjects who maintained a PASI 75 in period B and were on adalimumab in period A were re-randomized to adalimumab or placebo. Loss of response during Period C was defined in the Agency analysis as those subjects who did not maintain a score of at least minimal on PGA or a PASI 75 relative to baseline. Results of the Period C analysis demonstrated that of the patients who were maintained on adalimumab, 80/250 (32%) by PGA and 52/250 (20.8%) by PASI 75 had a loss of response. Patients who were switched to placebo had 173/240 (72.1%) by PGA and 138/240 (57.5%) by PASI 75 with

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a loss of response to earlier effective treatment. This latter evaluation demonstrated that Humira, even when given continuously fails to maintain up to a third of patients at a level of disease that is clear or minimal. Further, about 28% of patients may be maintained without further administration of Humira as demonstrated by those patients re-randomized to placebo (at least for the term studied).

It is not clear from the study, which patients would benefit from stopping Humira or whether those patients who stop use will have success with retreatment should there be a recurrence. This is something that will be requested of the applicant to explore further in a post-marketing study.

8. Safety

Due to safety concerns found during review, it is recommended that Humira be used for patients with psoriasis "when other systemic therapies are medically less appropriate." This is similar to the recommendation given for Remicade and is more restrictive than the current label for Enbrel.

Specific concerns included an increased occurrence of death in the clinical trials in patients randomized to receive Humira. While most of the specific instances of death associated with Humira use did not have a mechanistic correlation, the fact that all of the deaths occurred with Humira use and none with placebo was disconcerting and was discussed thoroughly by the clinical and safety review team. Evaluation of the post-marketing database revealed reports of death in patients with psoriasis or psoriatic arthritis who used Humira. Of comfort, little new findings specific to the psoriasis population were found when compared to that of the rheumatoid arthritis or Crohn's disease populations.

Humira is an immunosuppressant. Thus, there is increased risk of infection and increased risk of malignancy associated with Humira use. The risk of opportunistic infection is currently highlighted in the Humira label with a boxed warning. In addition, numerous warnings and precautions are presently described.

Six deaths occurred during the open-label portions of the adalimumab trials. The cause of death were cancer, cardiovascular events, suicide, and post-surgical complications from GI surgery. The relevance of some of these deaths due to Humira was questioned by the primary reviewer, with some focus on the immunosuppressive nature of Humira. Other TNF inhibitors, notably Remcade, has been implicated in exacerbation of congestive heart failure.

Post-market evaluation of Humira also revealed a number of deaths and hospitalizations reported in spontaneous adverse event reporting. Sixteen of those deaths were reported in patients who were being treated for either psoriasis or psoriatic arthritis.

From both the psoriasis studies and the post-market spontaneous adverse event reporting no new specific safety signals emerged that were not already included and described in labeling for Humira for indications already approved.

Of note Dr. Cook's recommendation that the Indication and Usage section include "when other systemic therapies are medically less appropriate" in effect asks that Humira be used as a second-line therapy and is similar in thinking, although less precise than the language used in the November, 2007 approval of Humira for plaque psoriasis in the EMEA: "Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to

respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA."

9. Advisory Committee Meeting

No Advisory Committee was held for this submission. Initial review during the filing period included consideration for an Advisory Committee. However, as this was an already approved drug product and other TNF-alpha inhibitors have been approved for the plaque psoriasis indication, the review team decided that this was not necessary for Humira. Remicade did go to a Regulatory Briefing when Centacor had applied for the plaque psoriasis indication. Thus, considerations could be gained from discussions for Remicade that could be applied to the Humira efficacy supplement application.

10. Pediatrics

According to the literature, only 37% of psoriasis patients first develop disease before the age of 20 and only 10% have some disease before age 10. In general, the disease is not severe or even of moderate severity in pediatric patients and does not warrant use of a systemic medication. Psoriasis is usually confined to localized cutaneous regions and is thus amenable to topical therapy.

Spontaneous remissions occur in pediatric patients for variable time periods making chronic immunosuppressive therapy with drugs such as TNF inhibitors less than desirable. Questions arise with regard to whether early immunosuppressive therapy will subject patients to later immune reactions to such therapies in later life, especially when used intermittently. In addition, it is not known if such therapies will interfere with vaccination and the developing immune system.

Quoting from Hurwitz's Clinical Pediatric Dermatology: "Most drugs given internally for psoriasis have potentially harmful side effects and should not, in general, be given to children with [psoriasis]."

On January 9, 2008, DDDP discussed with the PeRC that pediatric studies with Humira in plaque psoriasis should be waived in patients less than age 12 and deferred in 12 to 17 year olds pending the outcome of a mandatory post-marketing registry study report that was requested of the applicant as a condition of approval. Also pending is review by the Rheumatology team (DAARP) of an application for Juvenile Rheumatoid Arthritis. Upon further consideration and taking into consideration upcoming discussions for action regarding

☐ DDDP will waive pediatric studies with Humira in plaque psoriasis from 0 up to 4 years of age and will defer pediatric studies, including their design in patients 4 to 17 years until sufficient information is available regarding proposed study design and risk to study subjects and evaluation of adult long-term registry data as available. The sponsor's claims that the age group of 0 up to 4 years as not having sufficient numbers of patients and not being able to make accurate diagnoses of psoriasis in that age group is justified by current evaluation of literature. Literature was evaluated by this reviewer in the course of making this conclusion including studies conducted outside of the United States as far as prevalence and character of psoriasis in pediatric patients. The decision to defer patients from 4 to 17 years was due to information and regulatory discussion to be obtained during the upcoming review ☐ and public discussion with regard to post-marketing study needs in

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pediatric patients with plaque psoriasis. Pediatric plan for plaque psoriasis indication for Humira will need to be revisited in the future, which could be as soon as 2013, allowing 5 years of data to accumulate with at least 2 interim reports for the post-marketing commitment study and some evaluation of pediatric use with the approved indication in adults. It may be difficult to propose for a post-marketing registry to evaluate off-label use in pediatric subjects due to unintended consequences when promoting the registry.

11. Other Relevant Regulatory Issues

Not applicable to this review.

12. Labeling

With this efficacy supplement for plaque psoriasis, it was determined by the review team that there was a need for formalized patient communication to be had in the form of a mandatory Medication Guide. In a memo to the relevant OND Divisions, the Division of Drug Risk Evaluation (DDRE) in the Office of Surveillance and Epidemiology recommended that a Medication Guide be implemented for all of the TNF inhibitors due to risk of infection.

13. Recommendations/Risk Benefit Assessment

- Recommended regulatory action

The Clinical Team Leader recommends that Humira be approved for the indication of “the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy when other systemic therapies are medically less appropriate.”

- Risk Benefit Assessment

The review team had similar assessment of the risk benefit with Humira for the indication of chronic plaque psoriasis in adult patients. The Team Leader agrees with the risk benefit assessment made by the Primary Clinical Reviewer.

- Recommendation for Postmarketing Risk Management Activities

The Medication Guide should be implemented as discussed. A post-marketing registry study to assess the ongoing safety of this drug with prescribed for psoriasis patients receiving care in a setting outside of clinical studies is needed (see below).

- Recommendation for other Postmarketing Study Commitments

Three (3) clinical post-marketing commitments are requested:

- 1) The applicant should commit to conducting a long-term registry to evaluate the safety, e.g. risk of malignancy, infection, death and other serious adverse events. Current discussion with the applicant involves evaluation of these in a registry of 5,000 patients with follow up for at least annual reports.
- 2) The applicant should commit to a post-marketing study to evaluate the effect of retreatment with Humira, patients who were previously treated with Humira and then discontinued followed by a drug-free interval. Evaluations should include efficacy and whether there is any increased risk of developing anti-adalimumab antibodies.

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3) Pediatric use in plaque psoriasis patients age 4 to 17 years will need to be evaluated and a pediatric plan derived should further study in pediatric plaque psoriasis patients be needed. However, given the potential risk and immunosuppression of Humira, further study may not be warranted. The post-marketing commitment should be written to address deferral for age 4 to 17 years.

No additional post-marketing commitments were requested from other disciplines with this action.

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